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EXAMINER
GAMBEL, P

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CHRISTENSEN, O'CONNOR
JOHNSON & KINDNESS
2800 PACIFIC FIRST CENTRE
1420 FIFTH AVENUE
SEATTLE, WA 98101

DATE MAILED: 03/21/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 11/17/94 (3/16/95, 1/18/95) ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 30-33 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☑ Claims 1-29 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☑ Claims 30-33 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

15. Claims 1-29 are canceled.
Claims 30 is amended.
Claims 31-33 are added.
Claims 30-33 are pending.

REJECTIONS WHICH STILL REMAIN AND RESPONSE TO APPLICANT'S ARGUMENTS

17. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the form PTO-948 previously sent in Paper No. 4.

18. The previous rejection of claims 17-30 is withdrawn.

19. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure and failing to present the best mode contemplated by the applicant for carrying out the invention.

Applicant has not enabled the breadth of the claimed invention in view of the teachings of the specification. Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

A) Applicant has not disclosed how to use VCAM-specific antibodies therapeutically in humans. There is insufficient information or nexus to the in vivo operability of VCAM-specific antibodies to use applicant's invention.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3)(Tibtech, 1993). Humanized antibodies present serious problems with immunogenicity, since the idiotype of such antibodies will contain unique amino acid sequences. In referring to the related adhesion molecule family, Harlan states that whether you go humanized antibody, peptide, soluble receptor or saccharide, it still a long way to a product that would be appropriate for the clinical setting (Edgington, Biotechnology, 1992; see entire document particularly, page 386, column 3, paragraph 4). Furthermore, Pelletier et al. (J. Immunol., 1992) teach that VCAM-1-specific antibody therapy was not effective in inhibiting allograft rejection in a mouse model (see entire document). Simmons et al. (Blood, 1992) teach that the instant VCAM-1-specific antibody 6G10 did not block the binding of hemopoietic progenitors in vitro (see entire document, particularly page 394, column 1). Therapeutic indices of immunosuppressive drugs can be species- and model-dependent. Applicant has disclosed limited inhibitory data by the VCAM-specific antibody 6G10 under defined in vitro conditions. Applicant has not provided any evidence a priori that establishes the efficacy of the claimed invention for the treatment of human disease.

Therefore it does not appear that the asserted operability of the claimed method and compositions for modulating immune responses in humans would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone.

Applicant's arguments have been fully considered but are not found convincing. Applicant argues that the instant use of decreasing adhesion of bone marrow cells to bone marrow stromal cells is not the same as treating inflammatory diseases. Furthermore, applicant argues that Simmons et al. do teach 90% inhibition of human stem and progenitor cells, which would sufficient. On this issue, applicant appears to have taken the 90% value from the upper limits of the standard error of the mean, which does not necessarily reflect either the mean of the variance below the mean. Furthermore, Simmons et al. clearly state that it is significatnt that one was not able to completely block the binding of hemopoietic progentiros using either a combination of anti-$\alpha 4\beta 1$ and anti-VCAM antigbodies or using this antibody pair together with the EILDVPST peptide to investigate the role of fibronectin in this setting (page 394). It was concluded that the expresson by progenitors of any array of adhesion molecules with different ligand specficitiers might be anticipated givent the heterogeneity of stromal elements with the marrow microenvironment. The instant invention's exemplification of partial inhibition was done under well-defined culture conditions using a stromal cell line, which does not necessarily reflect the multifactorial regulation of hemopoietic cells and the hemopoietic microenvironment. Applicant appears to acknowledge the complexity associated with inflammation in vivo; applicant is invited to consider the same or similar order of complexity associated with hemopoiesis as it takes place in bone marrow, which was and still is well known in the art.

In addition, it is not clear what is the therapeutic benefit of decreasing adhesion of bone marrow cells to bone marrow stromal cells. The disclosure appears to indicate the use of the instant 6G10 antibody either to ameliorate inflammatory conditions (Summary of the Invention), the claims of which have been canceled; or to promote bone marrow transplantation (Example 5). How do the claimed methods promote bone marrow transplantation or hemopoiesis? As Simmons et al. discuss, the $\alpha 4\beta 1$/VCAM-1 interaction may promote the homing or attachment of primitive hemopoietic cells with the marrow after transplantation (page 394, column 2). It would seem that blocking hemopoietic stem/progenitor cells from interacting with stromal cells would impede engraftment, differentiation and self-renewal of donor hemopoiesis. For example, the administration of VLA-4-specific antibody (the counter-receptor to VCAM-1) can render human $CD34^+$ cells homeless (see Zanjani et al.; Blood, 1994). There appears to be no clear guidance in terms of how one would inhibit the interaction between bone marrow cells and bone marrow stromal cells in vivo and towards what therapeutic endpoint has been provided by the instant specification.

In a brief review of adhesion therapy, Shaffer relays similar concerns presented previously by the examiner about monoclonal antibodies, which are promising but involve toxicities and do not seem to have a lasting effect upon repeated use (Biotechnology Newswatch, 1993). Mountain et al. teach that most antibody-based therapies are very unlikely to achieve success with a single dose (Biotechnology and Genetic Engineering Reviews, 10: page 11, paragraph 1, first sentence, 1993). Murine antibodies are limited to one or perhaps two doses and the administration of further doses leads to accelerated clearance and in many cases to complete abrogation of efficacy (Mountain et al., pages 10-11, overlapping paragraph). Therefore, the success of multiple dosing with anti-adhesive antibodies as a therapeutic regimen would be highly questionable.

It is well known that in vitro experiments and animal models validate concepts based on studies of human disease. Modulation of cellular interactions is much easier to achieve under such controlled conditions than that experienced in the human hemopoiesis targeted by the claimed invention. In the absence of clear and convincing evidence commensurate in scope with the allegations and claims, applicant's arguments have not been found persuasive.

B) The previous objection/rejection set forth in section 22B is withdrawn in response to applicant's amended claims.

C) It is not clear from the specification whether 6G10-recognized molecules immunoprecipitated from TNF/IL-4 activated cultured human bone marrow stroma differ from VCAM (see specification, page 17, paragraph 1). These species include one with a molecular weight of 115-130 kD while the other was larger than 200 kD, as compared to the 100 kD of traditional VCAM-1. antigens recognized. Is the 115-130 kD species the seven domain (vs. six domain) VCAM structure? Is there any evidence of this? What is the greater than 200 kD structure? It appears that this antibody binds molecules other than the art-recognized VCAM. Therefore, the disclosure is not enabling for the antibody 6G10 to bind VCAM exclusively. Applicant has not set forth the metes and bounds of the target specificity of the 6G10 antibody, which was used to enable the instant invention. Therefore, it remains unclear whether the effects of 6G10 is mediated through VCAM alone or through multiple molecular species. The specification has not provided sufficient guidance to the specificity of the 6G10 antibody to enable the claimed invention's specificity for VCAM alone.

Applicant's arguments have been fully considered but are not found convincing. Applicant argues that the examiner's concerns over 6G10 is misplaced since the specification does show 6G10's binding of VCAM transfectants and the invention is drawn to targeting VCAM on marrow stromal cells. However, the specification discloses that the VCAM-specific antibody 4B9 did not bind human bone marrow stroma even though this antibody binds endothelium (page 17, lines 15-18). Here, applicant indicates that 6G10 binds an epitope distinct from 4B9. However, it is not clear that the inhibition of stromal interactions with bone marrow cells occurs via VCAM per se or through other (cross-reactive) moieties recognized by the 6G10 antibody and expressed by stromal cells. If 4B9 cannot inhibit such cellular interactions, it is possible that 6G10's inhibitory activity is occurring through one of the various molecular weight species disclosed and not necessarily through VCAM per se. Applicant's arguments have not been found persuasive.

21. Claims 30-33 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification (see sections 19-20).

22. The previous rejection of claims 17-30 under 35 U.S.C. § 112, first and second paragraphs, is withdrawn in response to applicant's cancellation and amendment of claims.

23. The previous rejection of claims 22-30 under 35 U.S.C. § 102(f) ~~have~~ has been withdrawn in response to the Masinovsky declaration under 37 C.F.R. § 1.132, filed 11/17/94.

24. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

25. Claims 30-31 are rejected under 35 U.S.C. § 103 as being unpatentable over Osborn et al. (1449, #029; Cell, 1989), Elices et al. (1449, #030; Cell, 1990), or Newman et al. (1449, #A1; U.S. Patent No. 5,011,778) in view of Graber et al. (J. Immunol., 1990), Rice et al. (1449, #028; Science, 1989), Rice et al. (J. Exp. Med., 1990), Lewinsohn et al. (Blood, 1990), Shimizu et al. (Immunol. Rev., 1990) or Prober et al. (1449, #014; Am. J. Pathol., 1988). Claims 30-31 are drawn to the modulation of VLA-VCAM cell interactions between bone marrow cells and marrow stromal cells by VCAM-specific antibodies.

Osborn et al. teach the expression of VCAM and its role as a cell adhesion molecule in normal tissue development and inflammatory conditions (see entire document). Osborn et al. also teach that VCAM-specific antibodies can block VLA-mediated binding and relate to this inflammatory responses (see page 1208, column 2). Osborn et al. also teaches that VCAM-dependent pathways would provide intervention points for correction of pathologies associated with acute and chronic inflammation. Elices et al. extend these observations to indicate that VLA-4 on leukocytes interacts with VCAM on endothelial cells and this can be blocked by antibodies (see entire document). Similarly, Elices et al. relate this interaction to normal and disease states involving leukocytes and their adhesion and recruitment. Newman et al. teach the use of 1E7/2G7-specific antibodies to inhibit leukocyte inflammatory responses (see entire document). As Graber et al. teaches, the 1E7/2G7 antigen is VCAM (see page 829, Note Added in Proof). Graber et al. is provided to indicate the 1E7/2G7 was VCAM and not to serve as prior art per se. These references differ from the claimed invention by not describing the 6G10 antibody or IL-4 activation per se. However, the specificity of the claimed intervention is VCAM and it would not have been critical to the targeting of the VCAM adhesion molecule that was activated through IL-4 or through other stimulants. Rice et al. (Science, 1989) teach the expression of INCAM-110 (VCAM) on endothelial cells and dendritic cells (see page 1305, column 1). Rice et al. (J. Exp. Med., 1990) extends this observation to localize INCAM-110 (VCAM) expression at inflammatory sites and on dendritic cells as well as its role in lymphocyte adhesion and activation (see entire document, particularly, page 1372, paragraph 3). Lewinsohn et al. teach the expression of adhesion molecules on human hemopoietic progenitor $CD34^+$ cells and draws attention to MEL-14, the murine analog of VLA (see entire document, particularly page 594). Shimuzu et al. review the art-known role of VLA-4 in T cell adhesion and stimulation and the identification of its ligand VCAM (see entire document, particularly pages 132-137 and Note Added in Proof). Prober et al. teach the art-known role of adhesion molecules in leukocyte adhesion and activation and the targeting of such interactions in manipulating pathologic diseases (see entire document).

Therefore, the art recognized the role of interfering adhesion interactions to modulate immune responses, including through VLA/VCAM pathways. VCAM was known to be present on endothelial cells and dendritic cells, both intimately involved in T cell adhesion and activation. VCAM's ligand VLA was known to be associated with either T cells or bone marrow precursors. The art teaches the generations of VCAM-specific reagents as taught by Osborn, et al., Elices et al. and Newman et al.; therefore the skilled artisan would have derived the claimed 6G10 antibody of the instant claims by routine experimentation. The skilled artisan would have used such VCAM-specific reagents to inhibit lymphocyte or hemopoietic interactions with VCAM-expressing cells to condition patients for hemopoietic reconstitution or various inflammatory conditions. One of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of VCAM-specific agents in a therapeutic regimen to modulate various inflammatory responses either in peripheral or central hemopoietic organs. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have been fully considered but are not found convincing. Applicant's arguments center on the issue that no reference teaches the existence of VCAM on bone marrow stroma cells and no reference discloses the presence of VLA-4 on bone marrow cells. To clarify an issue raised by the applicant concerning whether MEL-14 is the murine analog of VLA rather than L-selectin. It is the α chain of MEL-14 which is homologous to human VLA-4 (Holzmann et al., Cell, 1989; 1449, #02). Lewinsohn et al. clearly teach determining the expression of adhesion molecules on progenitor-stromal cell interactions in the hemopoietic microenvironment (see Discussion). Applicant is reminded of the broad scope of the claimed bone marrow cell and bone marrow stromal cell. Bone marrow cells comprises a number of cell types including T cells and their precursors for example. Further, it is noted that bone marrow cells comprise all the cells in the bone marrow, therefore hemopoieitic and stromal elements. Similarly, bone marrow stromal cells comprises a number of cell types including endothelial cells, fibroblasts, adipocytes and other elements. Applicant appears to be arguing limitations that are not claimed per se. Inhibiting an interaction between a bone marrow cell and a bone marrow stromal cell comprises inhibiting a T cell or its precursors from microvascular endothelial cells or dendritic cells. All such cells are in the bone marrow and all such cells would be targeted

in preparing a marrow transplant recipient with VCAM-specific antibodies for donor marrow engraftment and host marrow preparation (e.g. immunosuppression and providing space in the marrow microenvironment for engraftment). Applicant's arguments have not been found persuasive.

26. Claims 32-33 are rejected under 35 U.S.C. § 103 as being unpatentable over Osborn et al. (1449, #029; Cell, 1989), Elices et al. (1449, #030; Cell, 1990), or Newman et al. (1449, #A1; U.S. Patent No. 5,011,778) in view of Graber et al. (J. Immunol., 1990), Rice et al. (1449, #028; Science, 1989), Rice et al. (J. Exp. Med., 1990), Lewinsohn et al. (Blood, 1990), Shimizu et al. (Immunol. Rev., 1990) or Prober et al. (1449, #014; Am. J. Pathol., 1988) as applied to claims 30-31 above and in further view of Knapp et al. (Leukocyte Typing IV, 1989) and Hemler (Immunol. Today, 1988). Claims 32-33 are drawn to the modulation of VLA-VCAM cell interactions between $CD34^+$, stem and progenitor bone marrow cells and marrow stromal cells by VCAM-specific antibodies.

Osborn et al., Elices et al., Newman et al., Graber et al., Rice et al., Rice et al., Lewinsohn et al., Shimizu et al. and Prober et al. are taught supra in section 25. These references differ from the claimed limitations by not teaching the CD34, stem cell and progenitor cell aspects of the bone marrow cells being modulated. Shimizu et al. refers to the expression of VLA-4 on a wide variety of cells. Lewinsohn et al. clearly teach determining the expression of adhesion molecules on in progenitor-stromal cell interactions in the hemopoietic microenvironment (see Discussion).

It is noted that Knapp et al. and Hemler have been added to provide evidence of the known widespread expression of CD34 and VLA-4 (CDw49d) at the time the invention was made. For example, Knapp et al. teaches the expression of VLA-4α on a wide variety of cells included thymocytes, an immature T cell (i.e. progenitor cell). Applicant is invited to take note that Knapp et al. referes to the murine homologue of human VLA-4 functions as a Peyer's patch-specific lymphocyte homing receptor, citing Holzmann et al. Knapp et al. teach the expression of CD34 on progenitor cells and capillary endothelial cells. Hemler teaches that VLA-4 was present on most if not all hempoietic cels lines (Table 2). Although Hemler indicates that the bone marrow and thymus were not tested back in 1988, it was clear that this determination was under consideration at the time the invention was made. Therefore, the expression of VLA-4 and CD34 was known to be expressed on various tissues associated with hempoiesis in the bone marrow. It was known at the time the invention was made that VLA-4 operated through different receptor-ligand interactions, including VCAM. From the combined teachings of the

references, the ordinary artisan at the time the invention was made would have determined the contribution of adhesion molecules in the regulation of hemopoieis and how one could manipulate such interactions either for dissecting out critical interactions or for therapeutic manipulation, particularly in marrow transplantation, as presented above in section 25. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

26. No claim is allowed.

27. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

29. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. David Lacey can be reached on (703) 308-3535. The fax phone number for Group 180 is (703) 305-3014 or (703) 308-4227. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
Patent Examiner
March 15, 1995

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
3/20/95